

### **REMARKS**

The Examiner provides a number of objections and rejections. We list them here in the order in which they are addressed.

I. Claims 1, 9, 11-12 and 38-41 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Little *et al.* (U.S. Patent No. 6,207,370) in view of Garvin *et al.* (U.S. Patent No. 6,329,180) and further in view of Nakajima *et al.* and Hosfield *et al.*

II. Claims 1, 9, 11-13 and 38-41 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Little *et al.* (U.S. Patent No. 6,207,370) in view of Garvin *et al.* (U.S. Patent No. 6,329,180) further in view of Nakajima *et al.* and Hosfield *et al.* and further in view of Elion *et al.*

Applicants respond as follows:

**I. Claims 1, 9, 11-12 and 38-41 are not unpatentable under 35 U.S.C. §103(a).**

The Claims are rejected as obvious on the basis of a combination of Little *et al.*, Garvin *et al.*, Nakajima *et al.* and Hosfield *et al.*

The Applicants disagree and respectfully request that the Examiner point out exactly where Nakajima teaches, “more than one epitope marker can exist in a primer” (*Office Action*, p. 4, lines 3-4). As pointed out previously, the primers of Nakajima *et al.* very clearly contain a single epitope (i.e. c-myc). Furthermore, the Applicants again question what exactly is gained by the teaching of Hosfield *et al.* that “different epitope markers can exist in the same nucleic acid molecule together and be functional when expressed”. The problem is that an obviousness rejection cannot be based on elements randomly selected from a molecular toolbox. An obviousness rejection requires at least some demonstration that a person skilled in the art would make that combination. The KSR case has NOT excused examiners from providing a solid basis for combining art. The Federal Circuit, mindful of the KSR decision has indicated that a specific reason must be provided:

“While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry, the Court acknowledged the

importance of identifying “a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does” in an obviousness determination. *KSR*, 127 S.Ct. at 1731. Moreover, the Court indicated that there is “no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis.” *Id.* As long as the test is not applied as a “rigid and mandatory” formula, that test can provide “helpful insight” to an obviousness inquiry. *Id.*”

See *Takeda Chemical Industries v. Alphapharm Pty.*, 492 F. 3d 1350, 1357 (Fed. Cir. 2007). Moreover, *KSR* made it clear that conclusory statements are not enough and that there must be a “rational underpinning” to support obviousness:

“Often, it will be necessary ... to look to interrelated teachings of multiple patents ... in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit.” See, *In re Kahn*, 441 F.3d 977, 988 (CA Fed. 2006) (“[R]ejections on *obviousness grounds cannot be sustained by mere conclusory statements*; instead, there must be some articulated reasoning with some rational underpinning” to support the legal conclusion of obviousness”).

*KSR v. Teleflex*, Slip Op No. 04-1350 (April 30, 2007)(emphasis added). Thus, the Examiner cannot combine references without a “rational underpinning.” Moreover, if an applicant shows that the purported basis is not rational or properly based on the actual facts, the rejection cannot stand. With these rules in mind, Applicants now address the specific obviousness rejections.

The Examiner argues that a skilled artisan would find it obvious to combine primers comprised of nothing more than a single repeated c-myc domain (that do not bind a DNA template) with a cloning vector that contains different epitope markers in the same nucleic acid molecule. If this combination were obvious – which it is not – what result does the Examiner envision? The primers (Nakajima *et al.*) are not designed to anneal to a DNA target (again, they are designed to anneal to each other). The cloning vector (Hosfield *et al.*) is not designed for PCR amplification. Assuming for a moment that the primers of Nakajima *et al.* were capable of amplifying a DNA target other than themselves they would be completely incapable of producing a product with multiple epitopes – they are only capable of producing multiple epitopes when a DNA target is absent. How exactly would a skilled artisan find it obvious to combine primers that cannot anneal to (or amplify) a DNA template with a cloning vector that is not designed for PCR amplification? The combination with Hosfield *et al.* actually renders Nakajima *et al.* an even less effective reference (i.e. Hosfield *et al.* teaches away)!

Furthermore, since the primers of Nakajima *et al.* consist of only c-myc domains, a person skilled in the art would realize that they are only capable of amplifying a DNA target that already contains c-myc domains (i.e. the inverse complement of the c-myc primers). Since the present claims introduce epitopes this reference also teaches away from the combination that the Examiner alleges to be obvious.

The Applicants could continue to point out shortcomings of this combination of references, but that is not the burden in an obviousness rejection. The combination of Nakajima *et al.* and Hosfield *et al.* is not even plausible let alone obvious. Where there is no rationale basis by which a person skilled would find any motivation to combine these references, the rejection fails. The present rejection should be withdrawn.

## **II. The Applicants realize that the claims are not method claims.**

The Examiner alleges that the Applicant's traversal of the present combination is based on the intended use of the (faulty) primers.

Furthermore, Applicants are claiming a product, a reaction mixture containing two primers, not a method of using the primers. The intended use of the primers is not relevant. *Office Action, p. 5, lines 8-10.*

The Applicants are aware that language reciting intended use in composition claims is irrelevant. However, intended use language of the cited art is very relevant when relied upon by the Examiner to allegedly provide the motivation by which a skilled artisan would find a combination of references obvious. As demonstrated above, it is the functional language of these prior art references that demonstrates that the combination is not obvious; indeed it is the functional language of these prior art references that demonstrates that the combination could not possibly arrive at the presently claimed product.

## **III. The Examiner has failed to address the third epitope recited in the present claims.**

The Applicants further point out that even if a skilled artisan would find the present combination of references obvious (which requires ignoring the inability of the Nakajima primers to amplify the Hosfield template) the combination would still be silent on a third epitope marker as recited in the present claims. As described in the specification (for example page 44, lines 4-23 and page 49, line 25 to page 50, line 12), in some embodiments the third epitope (i.e.

C-terminal marker) is used to determine the fraction of protein that does not contain chain terminating or out-of-frame mutations - a purpose that the cited art does not even recognize. Clearly there is no basis for obviousness when an element is completely missing from the prior art and there is no reason for the prior art to suggest that one epitope (i.e. N-terminal marker) serves as an internal control to which another epitope (i.e. C-terminal marker) is normalized.

**III. Claims 1, 9, 11-13 and 38-41 are not unpatentable under 35 U.S.C. §103(a).**

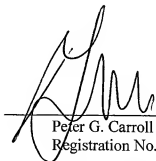
Based on the above arguments regarding the references Nakajima *et al.* and Hosfield *et al.*, the Applicants likewise contend that the rejection of Claims 1, 9, 11-13 and 38-41 based on a further combination with Elion should be withdrawn. Elion is only cited by the Examiner as allegedly teaching primers of certain lengths. Elion does not remedy the above-indicated deficiencies of the combination of Nakajima/Hosfield with Little/Garvin.

**CONCLUSION**

In view of the above arguments and amendments, the Applicants contend that Claims 1, 9, 11-13 and 38-41 are in condition for allowance. Should the Examiner believe a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned at 781.828.9870

Respectfully submitted,

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Peter G. Carroll  
Registration No. 32,837

MEDLEN & CARROLL, LLP  
101 Howard Street, Suite 350  
San Francisco, California 94105  
781-828-9870